REMARKS

All the claims submitted for examination in this application have been rejected on formal and substantive grounds. Applicants have amended their claims and respectfully submit that all the claims currently in this application are patentable over the rejection of record.

The first formal ground of rejection is the rejection of Claims 3-10. Claims 3-10 stand rejected, under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

Specifically, Claims 3-8 are directed to a method for measuring CYP3A levels and determining a dosage or sensitivity of the patient to nemorubicin. The Official Action argues that although the specification explains that the determination of CYP3A levels is accomplished by means of the erythromycin breath test (EBT) and that calculation for nemorubicin dosages are done by means of a "math formula", the specification never explains what the formula is or how the levels correlate to the dosages. The Official Action further submits that CYP3A metabolizes many types of drugs and therefore most studies have been done in the absence of other drugs also metabolized by CYP3A. The Official Action argues that applicants have not established how their invention would take into account conflicting medications.

Before addressing this first ground of rejection, applicants emphasize that independent Claims 1, 3, 5 and 7 have been amended to limit the method of treatment of a patient in need of a drug metabolized primarily by CYP3A, optimizing therapeutic efficacy, treating a cancer and predicting a patient sensitivity, respectively, to nemorubicin. It is parenthetically mentioned that dependent Claims 2, 4, 6 and 8, which limit the methods of Claims 1, 3, 5 and 7, respectively, to nemorubicin, have been cancelled.

Applicants respectfully submit that the specification enables all the amended claims currently in this application. The specification, at Page 2, lines 8 to 15, discloses that nemorubicin undergoes hepathic biotransformation into a more cytoxic metabolite. Insofar as these more cytoxic metabolites have been identified and their anti-tumor activity and toxicity have been tested, (see Page 3, line 20 to Page 4, line 7), and insofar as the abstract of the article, Baldwin et al., *Arch. Biochem. and Biophys., 409*:197-206 (2003), enclosed herewith as Exhibit A, establishes how nemorubicin (also known by MMDX), as set forth in the Baldwin et al. article, teaches the bioconversion of nemorubicin into a more potent and active metabolite this information emphasizes that one skilled in the art is enabled to use the EBT to practice the methods claimed in the present invention.

Experimental data show that this metabolite, formed through CYP3A, affects both anti-tumor activity and toxicity of nemorubicin. This is established in the specification at Page 4, line 7-10 as well as in the abstract of Quintieri et al., *Cancer Research, 60*:3232-3238 (June 15, 2000), enclosed herewith as Exhibit B.

As stated in the specification, nemorubicin is administered in a locoregional therapeutic approach to a patient with either a hepatic metastic cancer or previously untreated primary liver carcinoma. As set forth in the specification, evaluation of metabolizing activity of hepatic enzyme CYP3A is performed on a sample of patient plasma in order to select the proper amount of nemorubicin dosage that provides the best therapeutic treatment. Depending on the metabolizing activity ascertained, individual therapeutic dosage is defined for each patient.

Further proof that the present application is enabled is provided by published Abstract No. 1448 (Sun et al., *Proc. Am. Soc. Clin. Oncol., 22(abstract 1448)* (2003)) and Abstract No. 470 (Sun et al., *Euro. J. C. Supp., 2(8)*:143 (Sept. 2004)), attached herewith as

Exhibits C and D, respectively. These two publications teach that it is known that after intrahepatic locoregional administration, nemorubicin shows antitumor activity in a dosage range of from 200 to 600 mcg/m^2.

The second basis for the rejection under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, is the rejection of Claims 9 and 10. Insofar as Claims 9 and 10 have been cancelled, this ground of rejection is moot.

The third formal ground of rejection is again directed to Claims 9 and 10. Claims 9 and 10 stand rejected, under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. As in the case of the second formal ground of rejection, since Claims 9 and 10 have been cancelled, this ground of rejection is moot.

The final formal ground of rejection is directed to Claims 1, 2, 5, 6, 9 and 10. Claims 1, 2, 5, 6, 9 and 10 stand rejected, under 35 U.S.C. §112, second paragraph, as being indefinite.

Three separate bases for this ground of rejection are set forth in the outstanding Official Action. The first of these is directed to Claims 1 and 2. Claims 1 and 2 are deemed confusing since the treatment of a patient is never fulfilled by the claim which claims a process which only detects CYP3A levels but never administers anything to the patient.

As indicated above, Claims 1 and 2 have been combined so that the class of drugs metabolized primarily by CYP3A has been limited to nemorubicin. Suffice it to say, amended Claim 1 overcomes the indefiniteness rejection of record insofar as it adds a second step of administering a therapeutically effective amount of nemorubicin based on detected CYP3A levels. As such, the basis for this ground of rejection has been met and overcome by the amendment to Claim 1.

The second predicate for rejection under the indefiniteness clause of 35 U.S.C. §112 is the rejection of Claims 5 and 6. Claims 5 and 6 are directed to a method of treating cancer. The Official Action argues that those claims do not include a step in which a patient is treated with any drug.

As indicated above, Claims 5 and 6 have been combined so that the drug of original Claim 5 has been limited to nemorubicin. That claim, Claim 5, has been amended to include an additional step of administering a therapeutically effective amount of nemorubicin to the patient in need of that drug. As such, the basis for rejection, under 35 U.S.C. §112, second paragraph, of Claims 5 and 6 is removed.

It is emphasized that the aforementioned amendment to Claims 1 and 5, wherein a therapeutically effective amount of nemorubicin is administered to a patient in need thereof, is fully supported by the originally filed specification. Attention is directed to Page 4, lines 21-30. Therein it is recited that a method of treating a patient in need of treatment with a drug which is metabolized primarily by CYP3A, especially nemorubicin, is set forth. This disclosure is enough to support the introduction of the additional step of administering a therapeutically effective amount of nemorubicin in amended Claims 1 and 5.

Further support for this limitation is provided in the specification at Page 6, line 22 to Page 7, line 9. This portion of the specification specifically discloses the administration of nemorubicin to a patient by oral, parenteral or locoregional therapeutic approaches. Even more specifically, intrahepatic administration of nemorubicin via the hepatic artery is recommended.

The final basis for the indefiniteness rejection is directed to Claims 9 and 10. Insofar as these claims are cancelled, this ground of rejection is moot.

It is noted that four new claims have been added to this present application. New Claims 11-14 are respectively dependent from Claims 1, 3, 5 and 7. These claims point out that detection of CYP3A is obtained by an erythromycin breath test. Support for this limitation is provided in the originally filed application at Page 5, line 22 to Page 6, line 3 of the specification. These claims meet all formal requirements imposed under 35 U.S.C. §112.

Turning to the substantive grounds of rejection the first of these is directed to Claims 1, 3, 5, 7 and 9. Claims 1, 3, 5, 7 and 9 stand rejected, under 35 U.S.C. §102(b), as being anticipated by Collins, *Clin. Cancer Res.*, *6*:1203-1204 (2000).

Suffice it to say, Claims 1, 3, 5 and 7 have been amended to include therein the limitations of Claims 2, 4, 6 and 8, respectively. It is emphasized that the anticipatory rejection of record does not reject those claims over Collins. Since amended Claims 1, 3 and 5 represent Claims 2, 4 and 6 in independent form, it is apparent that this ground of rejection is overcome. That is, it is apparent that Collins makes no disclosure of utilizing nemorubicin in the methods defined by Claims 1, 3, 5 and 7.

The second substantive ground of rejection is the rejection of Claims 1-10, under 35 U.S.C. §103(a), as being unpatentable over Collins taken in view of Beulz-Riché et al., *Cancer Chemother Pharmacol*, *49*:274-280 (2002).

The Official Action admits that Collins teaches a method of testing CYP3A and predicting dosage levels but does not teach this use with nemorubicin. The Official Action thus argues that Beulz-Riché et al. teaches that nemorubicin (MMDX) is also metabolized by CYP3A, as well as docetaxel and other anti-cancer agents. The Official Action concludes that it would be obvious to one skilled in the art that since both docetaxel and nemorubicin are metabolized by CYP3A then the test that is commonly used to determine CYP3A levels and

predict dosages for docetaxel would also work for a similarily metabolized drug like nemorubicin. The Official Action avers that motivation for this equivalence is the common practice in cancer therapy to individualize dosages and thus it would be routine to use the test designed to optimize one drug on a similar drug that is also metabolized by CYP3A.

Admittedly, this ground of rejection is not moot by the amendment to the claims. Indeed, all the claims currently in this application are limited to methods in which the sole agent utilized is nemorubicin. However, the suggestion that structurally distinct compounds will act equivalently in medical practice is far removed from reality. If it is generally accepted that chemical results cannot be predicted, it is axiomatic that this principle applies to drug treatment of patients.

Moreover, applicants strongly argue that the teaching of Beulz-Riché et al. is not as suggested in the outstanding Official Action. What Beulz-Riché et al. discloses is the effect of paclitaxel, cyclosporine, cyclophosphamide, ifosfamide and tamoxifen on the metabolism of nemorubicin. Clearly, there is no disclosure or suggestion, by the combined teaching of Collins and Beulz-Riché et al., of the claimed method of treating a patient in need of a drug metabolized primarily by CYP3A, a method of optimizing therapeutic efficacy of nemorubicin, a method for treating cancer sensitive to nemorubicin or a method of predicting a patient sensitivity to nemorubicin by the combined teaching of Collins and Beulz-Riché et al.

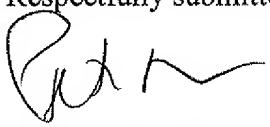
It is not understood how the Collins teaching of the use of the erythromycin breath test as a potential guide to individualized treatment with docetaxel can be combined with Beulz-Riché et al., which documents the effects of paclitaxel, cyclosporine, cyclophosphamide, ifosfamide and tamoxifen on the metabolism of nemorubicin, to make obvious the claimed

methods of Claims 1, 3, 5 and 7. Clearly, the combined teaching of Collins and Beulz-Riché et al. is not even remotely close to a disclosure of the methods of Claims 1, 3, 5, 7 and 11-14.

Reconsideration and removal of this substantive ground of rejection, in view of the above remarks, is therefore deemed appropriate. Such action is respectfully urged.

The above amendment and remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and the passage of issue of these claims, Claims 1, 3, 5, 7 and 11-14, is therefore respectfully solicited.

Respectfully submitted,



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Enclosure : Exhibits A-D

EXHIBIT A

Enclosure 2

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Identification of novel enzyme–prodrug combinations for use in cytochrome P450-based gene therapy for cancer

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Abstract

Gene-directed enzyme prodrug therapy can be used to increase the therapeutic activity of anti-cancer prodrugs that undergo liver cytochrome P450 (CYP)-catalyzed prodrug to active drug conversion. The present report describes a cell-culture-based assay to identify CYP gene–CYP prodrug combinations that generate bystander cytotoxic metabolites and that may potentially be useful for CYP-based gene therapy for cancer. A panel of rat liver microsomes, comprising distinct subsets of drug-inducible hepatic CYPs, was evaluated for prodrug activation in a four-day 9L gliosarcoma cell growth inhibition assay. A strong NADPH- and liver microsome-dependent increase in 9L cytotoxicity was observed for the CYP prodrugs cyclophosphamide, ifosfamide, and methoxymorpholinyl doxorubicin (MMDX) but not with three other CYP prodrugs, procarbazine, dacarbazine, and tamoxifen. MMDX activation was potentiated ~250-fold by liver microsomes from dexamethasone-induced rats (IC_{50} (MMDX) ~0.1 nM), suggesting that dexamethasone-inducible CYP3A enzymes contribute to activation of this novel anthracycline anti-tumor agent. This CYP3A dependence was verified in studies using liver microsomes from uninduced male and female rats and by using the CYP3A-selective inhibitors troleandomycin and ketoconazole. These findings highlight the advantages of using cell culture assays to identify novel CYP prodrug–CYP gene combinations that are characterized by production of cell-permeable, cytotoxic metabolites and that may potentially be incorporated into CYP-based gene therapies for cancer treatment.

Cytochrome P450 (CYP)[2] enzymes are endoplasmic reticulum-bound monooxygenases found in a variety of tissues, including the liver. These enzymes metabolize many lipophilic endogenous and xenobiotic substrates, including a large number of drugs and environmental chemicals [1,2]. The metabolism of drug substrates by CYP enzymes typically leads to drug inactivation and facilitates drug elimination. In some cases, however, CYP enzymes catalyze the activation of a comparatively nontoxic prodrug to form an active, cytotoxic drug metabolite. Examples of CYP prodrugs include the widely used anti-cancer alkylating agents cyclophosphamide (CPA) and ifosfamide (IFA) [3,4]. When activated in the liver, these anti-cancer CYP prodrugs are converted to reactive metabolites that circulate throughout the body and expose both tumor tissue and sensitive host cells to cytotoxic metabolites. A CYP-based prodrug activation strategy for cancer treatment has been introduced in an effort to increase therapeutic activity and reduce host toxicity associated with liver activation of these prodrugs [5,6]. The goal of this cancer gene therapy is to deliver a prodrug-activating CYP gene to cancer cells, enabling the formation of activated, cytotoxic metabolites directly within the tumor target, rather than in the liver. This may allow lower prodrug dosages to be employed, with correspondingly lower toxic side effects [7,8].

A significant problem with all gene therapy approaches, including CYP-based gene directed enzyme prodrug therapy (GDEPT), is the difficulty of achieving efficient expression of the therapeutic gene throughout

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[2] *Abbreviations used:* MMDX, 3′-deamino-3′-(2(*S*)-methoxy-4-morpholinyl); IFA, ifosfamide; CPA, cyclophosphamide; Dex, dexamethasone; BNF, β-naphthoflavone; PB, phenobarbital; TAO, troleandomycin (triacetyloleandomycin); GDEPT, gene-directed enzyme prodrug therapy; CYP, cytochrome P450; ER, estrogen receptor; Type II EBS, type II estrogen binding site; ddH_2O, distilled, deionized water.

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EXHIBIT B

Enclosure 3

[CANCER RESEARCH 60, 3232–3238, June 15, 2000]

In Vivo Antitumor Activity and Host Toxicity of Methoxymorpholinyl Doxorubicin: Role of Cytochrome P450 3A[1]

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ABSTRACT

Methoxymorpholinyl doxorubicin (MMDX; PNU 152243) is a promising doxorubicin derivative currently undergoing clinical evaluation. Previous *in vitro* studies suggested that the compound undergoes hepatic biotransformation by cytochrome P450 (CYP) 3A into a more cytotoxic metabolite(s). The present study examined the role of CYP3A-mediated metabolism in the *in vivo* antitumor activity and host toxicity of MMDX in the mouse model and investigated the potential for increasing the therapeutic effectiveness of the drug by inducing its hepatic CYP-catalyzed activation. We found that MMDX cytotoxicity for cultured M5076 tumor cells was potentiated 22-fold by preincubating the drug with NADPH-supplemented liver microsomes from untreated C57BL/6 female mice. A greater (50-fold) potentiation of MMDX cytotoxicity was observed after its preincubation with liver microsomes isolated from animals pretreated with the prototypical CYP3A inducer pregnenolone-16α-carbonitrile. In contrast, *in vivo* administration of the selective CYP3A inhibitor troleandomycin (TAO) reduced both potentiation of MMDX cytotoxicity and the rate of CYP3A-catalyzed *N*-demethylation of erythromycin by isolated liver microsomes (55.5 and 49% reduction, respectively). *In vivo* antitumor activity experiments revealed that TAO completely suppressed the ability of 90 μg/kg MMDX i.v., a dose close to the LD_{10}, to delay growth of s.c. M5076 tumors in C57BL/6 mice and to prolong survival of DBA/2 mice with disseminated L1210 leukemia. Moreover, TAO administration markedly inhibited the therapeutic efficacy of 90 μg/kg MMDX i.v. in mice bearing experimental M5076 liver metastases; a complete loss of MMDX activity was observed in liver metastases-bearing animals receiving 40 μg/kg MMDX i.v. plus TAO. However, pregnenolone-16α-carbonitrile pretreatment failed to enhance MMDX activity in mice bearing either s.c. M5076 tumors or experimental M5076 liver metastases. Additional experiments carried out in healthy C57BL/6 mice showed that TAO markedly inhibited MMDX-induced myelosuppression and protected the animals against lethal doses of MMDX. Taken together, these findings demonstrate that an active metabolite(s) of MMDX synthesized via CYP3A contributes significantly to its *in vivo* antitumor activity and host toxicity.

INTRODUCTION

DX[3] is a clinically effective, wide-spectrum antitumor agent, but its use is limited by the emergence of drug resistance and dose-related cardiomyopathy (1); consequently, several DX analogues have been synthesized. Among these, MMDX, a DX derivative bearing a methoxymorpholinyl group at position 3′ of the sugar moiety, has been selected for clinical evaluation in view of its activity against multidrug-resistant tumors *in vitro* and *in vivo* (2, 3) and lack of cardiotoxicity at therapeutic doses (4, 5).

MMDX is 80–150-fold more potent than DX when administered *in vivo* to mice, as revealed by both tumor growth delay and survival time assays (2, 3). Furthermore, its maximum tolerated dose, as defined on the basis of drug-induced myelosuppression in Phase I trials, is 50-fold lower than that of DX (5). In contrast, MMDX is only 2–10-fold more potent than DX *in vitro* against both tumor and hematopoietic cells (2, 6, 7). This discrepancy between MMDX cytotoxicity *in vitro* and *in vivo* suggests the generation of a more potent metabolite(s) *in vivo*. Accordingly, it was shown that preincubation of MMDX with human liver microsomes or rat liver S9 (9000 × *g* supernatant) fraction in the presence of NADPH markedly enhanced its cytotoxicity for cultured tumor cells (8–10); this metabolic process is antagonized by cyclosporin A and erythromycin, both of which are substrates/inhibitors of CYP enzymes belonging to the 3A subfamily (9, 10). A CYP3A-mediated liver microsomal potentiation was also demonstrated for morpholinyl DX, a closely related analogue of MMDX, but not for DX (11). Furthermore, enhancement of both MMDX and morpholinyl DX *in vitro* cytotoxicity by NADPH-supplemented liver microsomes or liver S9 fraction was shown to be associated with the formation of DNA interstrand cross-links (8, 10–12). To date, two hepatic MMDX metabolites exhibiting increased potency compared to the parent compound in *in vitro* and *in vivo* tumor growth inhibition assays have been identified; however, neither possesses DNA-alkylating activity (13).

The CYP enzymes constitute a large superfamily of heme-containing proteins that play a central role in the metabolism of a wide variety of endogenous compounds and foreign chemicals, including drugs (14). In mammals, the main drug-metabolizing families of CYP (CYP1, CYP2, and CYP3) are primarily expressed in the liver, although specific isoforms are present in some extrahepatic tissues (15). Members of the CYP3A subfamily are found in both experimental animals and humans and show similar molecular weight, immunochemical reactivity, and substrate specificity (14, 16). CYP3A4, the most abundantly expressed CYP enzyme in adult human liver, contributes to the oxidative metabolism of more than 60% of all clinically used drugs, including anticancer agents, such as cyclophosphamide, ifosfamide, paclitaxel, vinblastine, and epipodophyllotoxins (17–19). Moreover, CYP3A enzymes are expressed at different levels in human tumors (20–23), exhibit a highly variable hepatic expression (17), and can be inhibited or induced by a number of common drugs (24, 25); these characteristics may profoundly affect the activity and/or the host toxicity of antitumor agents that are substrates of these enzymes.

The aims of this study were to elucidate the contribution of CYP3A-mediated drug metabolism to the overall *in vivo* cytotoxicity of MMDX and to explore the potential for increasing MMDX activity by inducing its hepatic CYP3A-dependent bioactivation. Our findings in tumor-bearing and healthy mice strongly suggest that the MMDX active metabolite(s) synthesized by CYP3A contributes significantly to MMDX *in vivo* antitumor activity and host toxicity.

MATERIALS AND METHODS

Chemicals

MMDX was supplied as hydrochloride salt by Pharmacia & Upjohn (Nerviano, Italy). One mM stock solutions were prepared in sterile bidistilled water

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[3] The abbreviations used are: DX, doxorubicin; MMDX, 3′-deamino-3′-[2(*S*)-methoxy-4- morpholinyl]doxorubicin (methoxymorpholinyl doxorubicin; PNU 152243); CYP, cytochrome P450; PCN, pregnenolone-16α-carbonitrile; TAO, troleandomycin; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MST, median survival time; ILS, increase in life span.

EXHIBIT C

Enclosure 4

Phase I and pharmacokinetic study of nemorubicin hydrochloride (methoxymorpholino doxorubicin; PNU-152243) administered with iodinated oil via hepatic artery (IHA) to patients (pt) with unresectable hepatocellular carcinoma (HCC)

Sub-category: Hepatobiliary Cancer

Category: Gastrointestinal Cancer

Meeting: 2003 ASCO Annual Meeting

Abstract No: 1448

Citation: Proc Am Soc Clin Oncol 22: 2003 (abstr 1448)

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Abstract: Nemorubicin, a lipophilic doxorubicin derivative, is expected to be effective in liver neoplasms based on the observation of liver lesion regression in pts with colorectal, renal, breast cancer and HCC in phase I-II studies (Vasey, Cancer Research, 1995; de Takats, Proc ECCO 9, 1997), probably due to highly cytotoxic metabolite(s) produced by liver enzymes. The present study was conducted in China with nemorubicin administered IHA at 200, 400, 600, 800 mcg/m2 once every 8 weeks (q8wk). Maximal tolerated dose (MTD) was defined as ≥2/3 or 2/6 pt with dose-limiting toxicity (DLT): neutrophils < 0.5 x 109/L for ≥5 days and/or febrile neutropenia and/or platelets 25-50 x 109/L ≥5 days or < 25 x 109/L and/or ≥grade (gr) 3 non-hematological toxicity and/or gr 3 transaminitis/hyperbilirubinemia > 2 weeks or gr 4, and/or cardiomyopathy/unacceptable LVEF decline. Overall, 13 pt received 25 cycles (cy) and experienced mainly mild/moderate, reversible toxicities. Gr 3 events were thrombocytopenia (1/4 pt, 600 mcg/m2), vomiting (1/4 and 1/3 pt at 600 and 800 mcg/m2), diarrhea (1/3 pt, 400 mcg/m2), and transaminitis lasting < 2 weeks in 7 pt (11 cy), starting from 400 mcg/m2. No gr 4 events and no DLTs occurred at the doses studied. However, based on nemorubicin effects on transaminases, MTD was established at 800 mcg/m2 with gr 3 transaminitis in 2/3 pt. Protocol was amended to study a q6wk schedule at 200 and 600 mcg/m2. Eleven pt received 32 cy; tolerability was good (only reversible maximum gr 3 transaminitis in 1/5 pt at 200 and 2/6 pt at 600 mcg/m2; leucopenia in 1 pt at 200 mcg/m2). Overall, 6 partial responses were observed at: 200 (2), 600 (1) and 800 (1) mcg/m2 q8wk; 200 (1) and 600 (1) mcg/m2 q6wk. Nemorubicin showed a long terminal half-life (61-98h) and a high volume of distribution (1400-2300 L/m2). A phase II-III randomized study comparing IHA nemorubicin/iodinated oil vs mitomycin C in pt with HCC is ongoing.

EXHIBIT D

Poster Session: Anthracyclines
Friday 1 October, 2004

Enclosure 5

Abstract: 470

Citation: European Journal of Cancer Supplements Volume 2, No.8, September 2004, page 143

Efficacy of nemorubicin (MMDX) administered with iodinated oil via hepatic artery (IHA) to patients with unresectable primary hepatocellular carcinoma (HCC): phase II trial

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MMDX is a doxorubicin (DX) derivative with different mode of action, superior therapeutic activity including activity on multidrug resistance tumor models and improved tolerability (mainly reduced cardiotoxicity relative to DX). The past clinical experience by IV route evidenced a special affinity of MMDX for liver lesions, whose regression in pts with colorectal, renal, breast cancer were reported in Phase (Ph) I-II studies (Vasey, Cancer Res, 1995; de Takats, Proc ECCO 9, 1997). The specific antitumor activity may be due to the formation of highly cytotoxic metabolite(s) by liver enzymes. These findings prompted to test the efficacy of MMDX by IHA in HCC. Ph I studies were conducted in EU and in China. The encouraging efficacy and safety results (Sun, ASCO, 2003) were supportive of continuing the development in HCC.
A registrative ph II/III randomized study was started in China in 2002, with MMDX administered by IHA in iodinated oil at 600 mcg/m^2 every 8 weeks to chemotherapy-naive pts with unresectable HCC.
27 pts [25 male and 2 female (mean age 51.5, range 35-68 years); ECOG-PS 0 (21 pts) or 1 (6 pts); AJCC stage II (8 pts) and IIIA (19 pts); median number of cycles 2 (range 1-5)] were treated in the first stage of the Ph II portion of the study. 24 pts are currently evaluable for efficacy.
Partial remissions (PRs), evaluated by the WHO criteria occurred in 5/24 pts (4 confirmed) (RR = 20.8%; 95% c.i.: 7.1-42.2%).
Mild/moderate reversible neutropenia was reported in a small number of pts. Thrombocytopenia (Gr 3) occurred in 15% of pts (some pts were already thrombocytopenic at baseline). A mild/moderate SGOT/SGPT reversible increase occurred in 48% and 61% of cycles, respectively (max Gr 3 increase in 16% and 9.4% of cycles for SGOT and SGPT, respectively). No Gr 4 increase and no trend to cumulative liver toxicity with repeated administrations (neither in severity nor in frequency) were reported. Nausea and vomiting were also observed (Gr 3 vomiting in 11% of pts), being however mild/moderate in severity and resolving spontaneously in most cases without requiring antiemetic treatments. All the episodes recovered within 1 week. No Gr 4 gastrointestinal toxicity was observed. Other mild/moderate toxic manifestations were pyrexia, anorexia, and fatigue. No toxic deaths occurred during the trial.
In conclusion, MMDX shows good activity against HCC and is well tolerated, the majority of the events being of severity Gr 1 or 2 and reversible in all cases. Altogether, the objective responses observed in Ph I-II studies by IHA, indicate an overall RR of 24.5% (13 PRs/53 HCC pts; 95% c.i.; 13.7-38.3%), confirming a significant activity of MMDX in this disease. A manageable safety profile coupled with a wide therapeutic index (objective responses obtained also at 200 mcg/m^2) characterizes MMDX as a suitable compound for the IHA management of liver cancer.